REMARKS

Applicant wishes to thank Examiner Smith and Primary Examiner Marschel for their helpful suggestions and recommendations during the telephonic interview on June 12, 2003, in which the outstanding rejections were discussed in relation to the pending claims. As a result, Applicant submits this Amendment and Response.

Status of the claims

Claims 1-33 are pending in the application. Claims 30-33 have been withdrawn from consideration and claims 1-29 have been examined. Applicant hereby amends claims 1, 11, 15, 17, 18, 19 and 23. After entry of this paper claims 1-29 remain pending for examination.

Amendments to the Specification

Applicant has amended the specification to correct an inadvertent clerical error that resulted in the omission of the text for the abbreviation "MS-MS." The abbreviation "MS-MS" is well known to one of ordinary skill in the art and in the context of the present application one of ordinary skill in the art would readily understand the abbreviation to refer to tandem mass spectrometry. For example, the abbreviation MS-MS is so used in U.S. Patent No. 6,017,693 to Yates, III et al. at column 1, line 22. Accordingly, Applicant submits that this amendment adds no new matter.

Applicant has amended the specification to correct an inadvertent typographical or clerical error in equation 1. The error and support for the amendment is clear, for example, from the text of the paragraph containing equation 1; accordingly, no new matter is added.

In addition, per the Examiner's request, Applicant has amended the title and amended the inadvertent typographical and grammatical errors noted at page 43, line 14 and page 52, line 5. Applicant has also amended inadvertent typographical and grammatical errors at page 39, line 19 by insertion of "the" and at page52, line 23 by insertion of a period. No new matter is introduced by these amendments.

Amendments to the Claims

Applicant has amended claim 1. Support for the amendments to claim 1 is found at least at page 37, line 24, to page 38, line 2; and at page 39, lines 13-21. Accordingly, the amendment to claim 1 adds no new matter.

Applicant has amended claims 11, 17, 18, and 19 to further clarify their dependency from claim 1. Support for the amendments to claim 11 is found at least at page 29, lines 12-15; page 31, lines 1-6; and page 32, lines 15-29. Support for the amendments to claim 17 is found at least at page 29, lines 12-15; page 31, lines 1-6; and page 31, line 23, to page 32, line 14. Support for the amendments to claim 18 is found at least at page 29, lines 12-15; page 31, lines 1-22. Support for the amendments to claim 19 is found at least at page 29, lines 12-15; page 31, lines 1-6; and page 33, lines 1-27. Accordingly, the amendments to claims 11, 17, 18 and 19 add no new matter.

In accordance with the Examiner's suggestion, Applicant has amended claim 23 to provide the full name of the abbreviation in parentheses. The full name of the abbreviation in the context of the present application is well known in the art and support for this amendment is found throughout the specification; accordingly, no new matter is added.

Objections to the Disclosure and Title of the Application

Applicant wishes to thank the examiner for pointing out the typographical or grammatical errors at page 43, line 14 and page 52, line 5. Applicant has amended the specification to address these and other inadvertent typographical, clerical and grammatical errors in the specification.

In addition, per the Examiner's request, Applicant has amended the title to read "Methods for Mass Fingerprinting of Biomolecules."

Rejections Under 35 U.S.C. §112, second paragraph

Claims 1-29 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, the Office Action alleges that the abbreviation MS-MS appearing in claim 23 is vague and indefinite; that the terms "likelihood" and "likely" as used in the

claims are vague and indefinite; and that term "minimum number" appearing in claims 12 and 14 is vague and indefinite.

Applicant wishes to thank Examiner Smith and Primary Examiner Marschel for helping to clarify the issues in this rejection. Applicant shall address the abbreviation and the terms "likelihood," "likely" and "minimum number" in the phrases and context in which they appear.

The abbreviation "MS-MS"

Applicant submits that the abbreviation "MS-MS" is well known in the art as referring to tandem mass spectrometry. In addition, Applicant submits that one of ordinary skill would understand this abbreviation and what is claimed in original claim 23 in the context of the present application. Accordingly, Applicant submits that claim 23 is clear and definite.

Nevertheless, without acquiescing in the rejection, Applicant has amended claim 23 to amend in the full name and place the abbreviation in parenthesis. Applicant submits that amended claim 23 meets all the requirements of 35 U.S.C. § 112.

The term "detection likelihood"

Applicant submits that the term "detection likelihood" is clear as it appears in the claims and by examplification and discussion in the specification. Applicant submits that when this term is read in context by one of ordinary skill in the art in light of the specification it is neither vague nor indefinite. The term "detection likelihood" occurs in claims 1 and 23, which read, in part, as follows:

> wherein said mass signal corresponds to at least one biomolecule fragment of said potential source biomolecule
>
> determining a biomolecule fragment score for said mass signal, wherein said biomolecule fragment score comprises a function of a **detection likelihood** for said mass signal which defines a biomolecule fragment detection parameter;

(highlight of term added); and in claims 8 and 25, which depend, respectively, from claims 1 and 23, and read in part as follows:

> ...wherein the step of determining a biomolecule fragment score for said mass signal comprises the steps of:
>
> determining a **detection likelihood** for said mass signal which defines said biomolecule fragment detection parameter;

(highlight of term added). From the context of the claims, it is clear that the term "detection likelihood" refers to the likelihood of detecting a biomolecule fragment of a potential source biomolecule as a mass signal in a mass spectrum of a sample containing said biomolecule fragment. The clarity of the term "detection likelihood" is also supported by example and discussion in the specification.

For example, the specification at page 2, lines 22-26, explains,

> [T]he present invention is accomplished by explicitly taking into account the likelihood of detecting a biomolecule fragment as a mass signal in the mass spectrum of the sample. The numerical value associated with the likelihood of detecting a biomolecule fragment from a given biomolecule is referred to as a "biomolecule fragment detection parameter."

In addition, the specification discusses how a biomolecule fragment score can be a function of a detection likelihood for a mass signal, such as, for example, at page 11, lines 26-30:

> The biomolecule fragment score is a function of the biomolecule fragment detection parameter; i.e., the biomolecule fragment score is a function of the likelihood of detecting the matched biomolecule fragment as a fragment and/or digestion product of the associated potential source biomolecule with a given digest and a given mass spectrometry technique.

The specification also provides explicit non-limiting examples of a detection likelihood and how to determine a numerical value, referred to as the biomolecule fragment detection parameter, associated with a detection likelihood. The specification at least at page 21, line 10, to page 28, line 5, provides numerous non-limiting examples of obtaining numerical values for biomolecule fragment detection parameters and, it follows, examples and discussion of a detection likelihood for a mass signal.

For example, the specification at page 21, line 29, to page 30, line 20, makes clear to one of ordinary skill in the art that,

> An underlying principal to determining a biomolecule fragment detection parameter is that the numerical values of the parameters reflect the general relative mass signal intensity relationships between biomolecule fragments, and/or the fraction of a biomolecule fragment generally observed, in a mass spectrum of the sample or related samples that arise from differences in biomolecule fragment sequence and chemistry of the biomolecule fragmentation and/or digestion. ...
>
> The general relative intensity relationship can be determined by comparison of measured biomolecule fragment mass signal intensities generated from a sample of known biomolecule(s). Alternatively, the general relative intensity relationship can be determined from comparison of biomolecule fragment mass signal intensities predicted for a sample. ... The relative intensity relationship and fraction of a biomolecule fragment generally observed may be determined, for example, from published data or from data obtained by the investigator. An example of the latter such determination is illustrated below in Example 1 for an analysis employing a trypsin digest of proteins and a MALDI-TOF mass spectrometry technique.

(emphasis added).

Applicant thus respectfully submits that the term "detection likelihood" as set forth in each of claims 1, 8, 23 and 25 is clear and definite from the context of the respective claim and the specification.

Phrases containing the term "determining the likelihood"

It is Applicant's understanding that in the telephonic interview Primary Examiner Marschel suggested that the phrase "determining the likelihood of the presence or absence of said biomolecule based on said biomolecule score," as set forth in claim 1 could be further clarified by, for example, language indicating how a biomolecule score can be used to determine the likelihood of the presence or absence of said biomolecule.

Applicant submits that claim 1 clearly sets forth the metes and bounds of the invention claimed therein and that the specification provides an enabling disclosure of the step of "determining the likelihood of the presence or absence of said biomolecule based on said biomolecule score" in the context of the invention of claim 1 as a whole. For example, the specification at page 37, line 24, to page 38, line 2, states:

> The likelihood of the presence or absence of a biomolecule(s) in a sample is determined from the biomolecule scores of the potential source biomolecules. This likelihood may be determined by comparison of biomolecule scores calculated according to a single formulation, [or]... by cross comparison of biomolecule scores calculated according to at least two formulations

(emphasis added). The likelihood of the presence or absence of said biomolecule can also be determined by comparison to a biomolecule score value that serves as a scale or cut-off value, , e.g., such as provided by a biomolecule score obtained by offsetting the mass spectrum. For example, the specification at page 39, lines 13- 21, states,

> In one embodiment, the minimum biomolecule score which indicates a reliable determination that a biomolecule is likely present is determined by offsetting the entire mass scale of the mass spectrum. ... Accordingly, where [the] biomolecule score increases with presence likelihood, the maximum biomolecule score obtained by such offsetting represents the biomolecule score below which biomolecules cannot reliably be said to be likely present in the sample.

Accordingly, Applicant submits that one of ordinary skill in the art would understand the phrase "determining the likelihood of the presence or absence of said biomolecule based on said biomolecule score," and what is claimed in claim 1 in light of the specification. As a result, Applicant submits that the phrase "determining the likelihood of the presence or absence of said biomolecule based on said biomolecule score," as set forth in claim 1, meets the requirements of 35 U.S.C. § 112, second paragraph. See MPEP §2173.05(b) (Eighth Edition, August 2001).

Nevertheless, without acquiescing in the rejection, Applicant has amended claim 1 such that the determining step now reads as,

> determining the likelihood of the presence or absence of said biomolecule based on a comparison of said biomolecule score of said potential source biomolecule that corresponds to said biomolecule to at least one other biomolecule score

where new text has been underlined. Applicant submits that amended claim 1 is clear, definite and meets the requirements of 35 U.S.C. § 112.

The term "determining the likelihood" also appears in the body of claims 11, 17, 18, 19 and 21. Applicant submits that claims 11, 17, 18, 19 and 21 are clear and definite

and one of ordinary skill in the art would understand what is claimed in each of these claims in light of the specification. The term "determining the likelihood" occurs in the body of claims 11 as follows;

> calculating a weighted biomolecule score for said potential source biomolecule from said biomolecule score and said relative biomolecule match count; and
> determining the likelihood of the presence or absence of said biomolecule based on said weighted biomolecule score,

in the body of claim 17 as follows;

> determining the likelihood of the presence or absence of said biomolecule based on said relative biomolecule intensity,

in the body claim 18 as follows;

> determining the likelihood of the presence or absence of said biomolecule based on said relative biomolecule detection parameter,

and in the body of claim 19 as follows;

> determining the likelihood of the presence or absence of said biomolecule based on said biomolecule mass error.

Applicants submit that claims 11, 17, 18, and 19 are clear and definite because one of ordinary skill in the art would understand what is claimed in each of these claims in light of the specification. For example, the specification makes clear at page 29, lines 12-15, that,

> In one embodiment, the biomolecule score is equal to a base numerical value (determined in step 4100) weighted by another numerical value or values (see step 4300 and steps 4400 to 4700).

and at page 31, lines 1-6, that,

> In one embodiment, ("YES" to test 4300) the biomolecule score base value is weighted by at least one numerical value that reflects supplementary information on the likelihood that the potential source biomolecule is present in, or absent from, the sample.

Accordingly, one ordinary skill in the art would understand that one non-limiting enabling example of a weighted biomolecule score a calculated from: (1) a biomolecule score and a relative biomolecule match count, as encompassed by claim 11, is given at least at page

32, lines 15-29; (2) a biomolecule score and a relative biomolecule intensity, as encompassed by claim 17, is given at least at page 31, line 23, to page 32, line 14; (3) a biomolecule score and a relative biomolecule detection parameter, as encompassed by claim 18, is given at least at page 31, lines 6-22; and (4) a biomolecule score and a relative biomolecule mass error, as encompassed by claim 19, is given at least at page 33, lines 1-27. As a result, Applicant submits that the term "determining the likelihood" is clear and definite in each of claims 11, 17, 18 and 19.

With respect to claim 21, Applicant submits that this claim is clear and definite on its face and in context with relation to claim 1 from which it depends. Claim 21 reads,

> The method of claim 1 wherein said step of determining the likelihood of the presence or absence of said biomolecule comprises determining the likelihood of the presence or absence of a protein.

and further defines the determining step of claim 1 in a clear and definite manner. Accordingly, claim 21 is clear and definite because the determining step of claim 1 is clear and definite.

Nevertheless, without acquiescing in the rejection, Applicant has amended claims 11, 17, 18 and 19 to further clarify their dependencies from claim 1. Applicant submits that each of amended claims 11, 17, 18 and 19 and unamended claim 21 are clear and definite and that the specification provides an enabling disclosure of these claims. Applicant thus submits that one of ordinary skill in the art would understand the term "determining the likelihood" as it appears in amended claims 11, 17, 18, 19 and unamended claim 21 and what is claimed in these respective claim in light of the specification. Accordingly, Applicant submits that each of amended claims 11, 17, 18, 19 and unamended claim 21 meet the requirements of 35 U.S.C. § 112.

The term "likelihood" in claim preambles

The term "likelihood" appears in the preamble of claims 1, 2, and 23. To the extent the rejection under 35 U.S.C. § 112, second paragraph, is applied to these appearances of this term, Applicant submits these appearances do not render claims 1, 2 and 23 either vague or indefinite.

Specifically, to the extent the Office Action reasons that because the term "likelihood" can be vague and indefinite, claim preambles containing such terms are necessarily vague and indefinite, Applicant must respectfully disagree. The term "likelihood" must be read in the context in which it appears and whether one of ordinary skill in the art would understand what is claimed in light of the specification. See MPEP §2173.05(b) (Eighth Edition, August 2001). Applicant submits that when the term "likelihood" is read in the context of the respective claim as a whole, the term is both clear and definite.

The term "likely" and the phrase "determining that said biomolecule is likely absent if"

The term "likely" occurs in claims 2, 12, 13 and 14, in the phrase "determining that said biomolecule is likely absent if." It is Applicant's understanding that in the telephonic interview Primary Examiner Marschel indicated that on further consideration the term "likely" was clear and definite in the context in which it appears in each of claims 2, 12 and 14 because, for example, of the language following the conjunction "if" in the phrases in which the term "likely" appears.

Accordingly, Applicant submits that the term "likely" as it appears respectively in claims 2, 12, 13 and 14 is clear and definite. In addition, Applicant notes that the term "likely" as it appears respectively in claims 1, 12, 13 and 14, in the phrase "determining that said biomolecule is likely absent if" is further supported by examplifcation and discussion in the specification. For example, further support for this term is found in non-limiting descriptions at least at page 40, lines 6-18, with respect to claim 2; at least at page 38, lines 16-26, with respect to claim 12; at least at page 35, lines 1-19, with respect to claim 13; and at least at page 38, line 27, to page 39, line 12, with respect to claim 14.

The term "minimum number"

Applicant submits that one of ordinary skill in the art would understand what is claimed in each of the claims containing the term "minimum number" in light of the examplification and discussion of this term in the specification. Accordingly, Applicant submits that the term "minimum number" as it appears respectively in claims 12, 14 and 15 is clear and definite.

The term "detection likelihood" occurs in claim 12 which reads, in part, as follows;

> determining that said biomolecule is likely absent if said biomolecule fragment count of the corresponding potential source biomolecule is lower than a **minimum number**

; in claim 14 which reads, in part, as follows;

> determining that said biomolecule is likely absent if said intense biomolecule fragment count of the corresponding potential source biomolecule is lower than a **minimum number**

; and in amended claim 15 which reads, in part, as follows;

> identifying from about 100 to about 200 of the most intense mass signals with a said mass error less than said mass tolerance value and a biomolecule fragment detection parameter greater than a **minimum number** to determine the intense mass signals.

(highlight of term added).

Applicant submits that the term "minimum number" as it appears respectively in claims 12, 14 and 15 is supported by examplifcation and discussion in the specification. For example, support for this term is found in non-limiting descriptions at least at page 38, line 16, to page 39, line 12, with respect to claims 12 and 14; and at least at page 18, lines 6-21, with respect to amended claim 15. As a result, in light of the specification one of ordinary skill in the art would be able to understand what is claimed respectively in claims 12, 14 and 15. Accordingly, Applicant submits that the term "minimum number" as it appears respectively in claims 12, 14 and amended claim 15 is clear and definite.

Rejections Under 35 U.S.C. §102(a)

Claims 1, 4, 7, 21-24, and 28-29 were rejected under 35 U.S.C. §102(a) as allegedly anticipated by U.S. Patent No. 6,017,693 to Yates, III et al., ("Yates"). Specifically, the Office Action at pages 4-5, reads:

> Yates, III et al. disclose a mass tolerance of the unknown peptide from which spectra from known sequences are identified if they fall within the tolerance amount (col. 4, lines 59-67 and Figure 4) which is reasonably interpreted as the biological [sic] fragment detection parameter. Yates III et al. disclose an example using a tolerance of + 0.05% of the mass of the unknown peptide used (col. 5, lines 25-26)

> which is reasonably interpreted as a detection efficiency as stated in claims 7 and 24.

Applicant respectfully submits that Yates does not teach or suggest every element of Applicant's independent amended claims 1 and 23 or either of these claims as a whole. Specifically, Yates does not teach or suggest a method for determining the likelihood of the presence of a biomolecule using a "biomolecule fragment detection parameter" as set forth in either amended claim 1 or 23.

In particular, the specification (for example, at page 2, lines 22-26) makes clear to one of ordinary skill in the art that the "biomolecule fragment detection parameter,"

> [takes] into account the likelihood of detecting a biomolecule fragment as a mass signal in the mass spectrum of the sample. The numerical value associated with the likelihood of detecting a biomolecule fragment from a given biomolecule is referred to as a "biomolecule fragment detection parameter."

(emphasis added, quotations in original). The specification further describes (for example at page 21, line 30, to page 30, line 5) that

> the numerical values of the [biomolecule fragment detection] parameters reflect the general relative mass signal intensity relationships between biomolecule fragments, and/or the fraction of a biomolecule fragment generally observed, in a mass spectrum of the sample or related samples that arise from differences in biomolecule fragment sequence and chemistry of the biomolecule fragmentation and/or digestion

(emphasis added) and describe (for example, at page 30, lines 10-20) how the general intensity relationships can be determined:

> The general relative intensity relationship can be determined by comparison of measured biomolecule fragment mass signal intensities generated from a sample of known biomolecule(s). Alternatively, the general relative intensity relationship can be determined from comparison of biomolecule fragment mass signal intensities predicted for a sample. ... The relative intensity relationship and fraction of a biomolecule fragment generally observed may be determined, for example, from published data or from data obtained by the investigator. An example of the latter such determination is illustrated below in Example 1 for an analysis employing a trypsin digest of proteins and a MALDI-TOF mass spectrometry technique.

(emphasis added).

For example, a biomolecule fragment detection parameter can be determined by comparison of measured biomolecule fragment mass signal intensities generated from a sample of known biomolecules. For example, if a known sample of biomolecules contain a concentration X of peptide A, and the measured intensity of the mass signal for A in a mass spectrum of the known sample corresponds to a concentration Y; the relative intensity relationship in this example is X/Y.

Accordingly, the specification makes clear that a biomolecule fragment detection parameter, of the present invention, reflects the general relative mass signal intensity relationships that arise from differences in the likelihood of detecting different biomolecule fragments as a mass signal in the mass spectrum of the sample.

In contrast, the mass tolerance approach used by Yates (e.g., col. 4, lines 59-67 and Figure 4) does not take into account the likelihood of detecting a peptide as a mass signal in the mass spectrum of a sample containing that peptide or reflect general relative mass signal intensity relationships. Rather, the mass tolerance approach of Yates merely takes into account the reliability of a match between a measured mass signal and a mass signal in a known spectra based on differences in mass. Applicant thus submits that Yates does not teach or suggest a "biomolecule fragment detection parameter" or its use as set forth in Applicant's claims. As a result, Applicant submits that claims 1 and 23, and claims 2-22 and 24-29 that depend respectively therefrom, are novel and non-obvious over Yates.

In addition, Applicant must respectfully disagree that a mass tolerance can be reasonably interpreted as a detection efficiency as set forth in Applicant's claims 7 and 24, or as the term detection efficiency is normally used in the art. Specifically, a mass tolerance is a measure of accuracy and/or precision but not efficiency. As a purely illustrative example of the common use of these terms, a mass spectrometer that detects 90 of a 100 ions of mass 100 amu would have a detection efficiency of 90% for that mass. However, if, for example, a known sample of mass 100 amu shows up at 101 amu in the mass spectrum, the mass spectrometer could be said to be no more accurate than 1 amu, and such an instrument would not meet a mass tolerance of less than 1 amu. Accordingly, Applicant respectfully submits that Yate's example of using a tolerance of + 0.05% of the

mass of the unknown peptide used (e.g., col. 5, lines 25-26) cannot be reasonably interpreted as a detection efficiency as set forth in Applicant's claims 7 and 24.

Rejections Under 35 U.S.C. §103

Claims 1-7, 11-17, 21-24, and 28-29 were rejected under 35 U.S.C. §103 as allegedly obvious over Yates in view of U.S. Patent No. 5,710,713 to Wright et al. ("Wright"), and the article "*Improving protein identification from peptide mass fingerprinting through a parameterized multi-level scoring algorithm and optimized peak detection*" in Electrophoresis 1999, Volume 20, pages 3535-3550 by Gras et al. ("Gras").

Applicant respectfully submits that Yates, Wright, and Gras, either alone or in proper combination, fail to teach or suggest all elements of Applicant's claims or these claims as a whole. As discussed above, Yates fails to teach or suggest using a "biomolecule fragment detection parameter" as set forth in either amended independent claim 1 or 23, and Wright and Gras, either alone or in proper combination, do not provide the teaching missing in Yates.

Specifically, neither Wright nor Gras teach using a "biomolecule fragment detection parameter" as set forth in either amended independent claim 1 or 23. In addition, Applicant notes that the Office Action does not appear to assert that either Wright or Gras in combination with Yates renders claim 1 or 23 obvious. Applicant thus respectfully submits that claims 1 and 23, and claims 2-22 and 24-29 that depend respectively therefrom, are novel and non-obvious Yates, Wright, and Gras, either alone or in proper combination.

CONCLUSION

In view of the amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone call would expedite the prosecution of this case, the Examiner is invited to call the undersigned at (508) 416-2472.

Respectfully submitted,
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